American Chemistry Council
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Presentation on the

NTP Technical Report on the Toxicology and Carcinogenesis Studies of MIBK

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September 27-28, 2005

ACC Comments on NTP MIBK Bioassay Report

- Comments are provided by ACC Ketones Panel, representing US manufacturers of MIBK
- We do not disagree with the basic findings of the draft report
- We propose revisions to sections of the text to make it more useful to potential users of the final report

Report incompletely addresses tumor response in animals

- The studies appear to be well-conducted and the presentation of tumor data accurate
- We understand NTP reports address only findings in animals, and not potential relevance of findings to humans
- Report is likely to be used for cancer classification, and possible quantitative risk assessment

Additions to text may aid ultimate user

- We request that certain sections of the text be modified to more fully characterize the tumor response
- Report will be more useful for ultimate user – regulator, industry or the public
- We have submitted detailed written comments: provide an overview here

Two significant tumor findings

- Male rat kidney and mouse liver tumors are only significant tumors induced by MIBK
- Both tumor types were predicted based on known effects of MIBK in rats and mice
- Text of report suggests further work is needed to address mode of kidney tumors, and there is no discussion of mode of liver tumors

Male rat kidney tumor MOA

- Mode of action [MOA] is either induction of hyaline droplets and alpha-2-microglobulin [a2u], or enhancement of chronic progressive nephropathy [CPN], or both.
- SAR with other oxygenated solvents confirm
- Text should more fully discuss the substantial literature on related materials acting by this MOA, and conclusions regarding relevance for humans
- More research to identify a2u accumulation is unnecessary

Mouse liver tumors are adenomas, not carcinomas

- Modify text to indicate tumor increase over high background incidence is due to increase in adenomas, not in carcinomas, indicating a lack of tumor progression
- Decrease in carcinomas in males!
- Slight increase in carcinomas in females only at top dose, which appeared to exceed the MTD [based on >10% decrease in body weight gain]
- Decrease in carcinomas metastasizing to lung

Mouse liver tumor MOA

- Add discussion of mode[s] of action of adenomas
- MIBK is an inducer of hepatic mixed function oxidase [MFO]
- Other materials that induce MFO increase mouse liver adenomas by increasing clonal expansion of endogenous mouse liver preneoplastic foci
- No evidence for other MOA, such as genotoxicity, hepatotoxicity, oxidative stress, peroxisomal proliferation
- MOA not relevant for extrapolation to humans

Summary

- Study is well designed and conducted
- Tumor response should be more extensively discussed in context of all available data
- Discussion of possible modes of action would aid a better understanding of the relevance of the findings to humans
- Expanded discussion would maximize the benefit of the report to the end user – both the regulator and the regulated - as well as the public